The burden of knowing
By Phil Jones

Is it a privilege, or is it a burden, to have knowledge of what may lie ahead?

Modern medicine brings with it many advantages for modern societies, but – for some people – those advantages also have associated personal costs. One such cost flows from developments in genetics, whereby conditions that might previously not even have been recognised can now be identified and documented ... and their likely effect on individuals predicted with increasing levels of confidence and accuracy.

In 1993 an extensive study of 57 adult members of a French family identified a new genetically-based medical condition – still relatively unknown, even today – that came to be called CADASIL. Within three years, the responsible gene was identified. During the past twenty or so years, over 1,000 CADASIL families have been identified worldwide and over 1,000 scientific articles published on their experiences.¹

So, what is CADASIL? It’s not too hard to guess that it’s an acronym: Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy. Deconstructing the acronym is helpful because of its less familiar terms:

- **Cerebral** – pertaining to the cerebrum or brain;
- **Autosomal** – a trait or disorder that can be inherited. If a gene is autosomal dominant, a person only need get it from one parent in order for offspring to inherit the condition;
- **Dominant** – a disease of the arteries, usually those of small to medium size;
- **Sub-cortical Infarcts** – areas of tissue death in the subcortical region of the brain (i.e. immediately below the cerebral cortex). White matter and deep grey structures constitute the subcortical region. This is the area involved in thought, voluntary muscle movement, reasoning and memory;
- **Leukoencephalopathy** – a brain disease caused by damage to the white matter.

Put simply, CADASIL is an inherited condition that causes strokes and related impairments. The cause of the condition is a mutation on the Notch 3 gene, which – after birth – has a key role in maintaining the integrity of arterial vessel walls. The mutation (the specific form of which may vary) causes muscle cells in the arterial wall to disintegrate over time, leading to a loss of blood supply in the region supplied by the blood vessel concerned. Arteries throughout the body may be affected, but it is vessels within the brain where the effects of the mutation manifest themselves most seriously. The white matter and deeper parts of the brain are particularly affected, giving rise to the eponymous infarcts of the condition.

An infarct in the brain can lead to a stroke, which is often the symptom with which CADASIL patients first present. In individuals with CADASIL, a stroke can occur at any time from childhood to late adulthood, but typically happens during mid-adulthood. Further, not only does the age of symptomatic onset vary greatly amongst affected individuals, but so does the severity of symptoms.

¹ The disease was actually first described by a Belgian neurologist in 1955. In 1987, a Nordic case was identified and reported upon. At the time, the condition was generally referred to as hereditary multi-infarct dementia.
People with CADASIL often have more than one stroke in their lifetime; and recurrent strokes can cause cumulative damage. Strokes that occur in the subcortical region of the brain can cause progressive loss of intellectual function (i.e. dementia) as well as changes in mood and personality.

The damaged blood vessels can also lead to some patients experiencing migraines, often with visual sensations or auras, or – though less often – recurrent seizures (epilepsy). Many CADASIL patients also develop leukoencephalopathy, a change in white matter tissue that can be seen with magnetic resonance imaging (MRI). Death generally occurs 10-20 years after the onset of strokes and dementia, typically in the sixth decade, though some patients survive well beyond this.

If one parent is affected, each child of that parent has a 50% chance of inheriting the condition. But, once a child receives the abnormal copy of the gene, the child is certain to develop CADASIL. Although a gene mutation may occur spontaneously, most individuals with CADASIL have a family history of the condition. However, because a genetic test for CADASIL was not available before 2000, many cases were previously misdiagnosed as multiple sclerosis, Alzheimer's disease, or some other neurodegenerative disease.

CADASIL is not associated with the common risk factors for stroke and heart attack, such as high blood pressure and high cholesterol, although some affected individuals might, of course, also have these health problems. Because it is a rare and little known condition, it is often under-recognized and under-diagnosed. Accordingly, the condition may be suggested by a patient presenting with one or more of the following factors:

(i) One or more of recurrent subcortical ischemic strokes (especially before age 60 and in the absence of vascular risk factors), migraine (especially with aura) and/or early cognitive decline or subcortical dementia;
(ii) An MRI image showing more white matter lesions in the brain than might be expected for the patient’s age (characteristic changes to white matter are detectable before an affected person is in his or her twenties);
(iii) a family history of migraine, early-onset stroke, or dementia. The clinical spectrum of CADASIL is broad, and – in some families – migraine may be the only clinical manifestation.

While MRI is not used to diagnose CADASIL with certainty, it can show the characteristic progression of white matter changes decades before onset of symptoms. Once CADASIL is suspected, however, confirmation requires genetic testing, which can nowadays be undertaken simply by using a blood sample.

There is currently no cure for the condition, and medical treatment is aimed at minimising risk factors. Migraine headaches may be treated by appropriate drugs, and a daily aspirin may reduce stroke and heart attack risk. Typically, aspirin and statin therapy will be used jointly. Homocysteine levels tend to be elevated in CADASIL patients and treatment with folic acid is sometimes considered.\(^2\) Anticoagulation drugs are generally inadvisable because of the ongoing risk of micro-haemorrhages. Other stroke risk factors such as smoking, hypertension and high blood fats should also be treated. Symptoms usually progress slowly. By the age of 65, however, most people with CADASIL will have some cognitive problems and dementia, and some will become dependent following multiple strokes.

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\(^2\) Homocysteine is an amino acid in the blood. High levels have been associated with atherosclerosis (fatty deposits in blood vessels) although a causal link has not been established. Folic acid interacts with homocysteine in such a way as to reduce its associated risk.
In my own family, the effects of CADASIL can be traced, in all probability, to at least my great-great grandmother, who died in 1877 at the age of 41 because of “Softening of Brain [and] Convulsions”. Following the genetic line, my grandmother died in 1960 at the age of 54 as a result of “Disseminated Sclerosis” (i.e. Multiple Sclerosis). My mother died in 2001 at the age of 69 because of “Cerebrovascular accidents [and] TIA’s”; and her younger sister predeceased her after suffering the same fate at the age of 65. Of some comfort, perhaps, is that my great-grandmother, who must have passed on the faulty gene, survived until age 78. She died in 1947 of “Myocardial degeneration [and] Arterio Sclerosis”, which is consistent with having the gene, despite living to a reasonable old age (though her physical and mental condition prior to death is unknown).

My own confrontation with CADASIL came two years ago at the age of 60, following an unexplained brain haemorrhage. There was, at the time, some debate amongst the hospital doctors as to whether an MRI was necessary, given that a CT scan had already confirmed a bleed in the brain. But some of the more prescient consultants took the view that the unusual locus of the haemorrhage (the cerebellar vermis), coupled with an absence of established risk factors, warranted further investigation. In the event, the MRI revealed abnormal signals in the sub-cortical white matter, the distribution of which was characteristic of CADASIL. A genetic blood test later confirmed the diagnosis.\footnote{The genetic test found what was described as a “classic well described mutation”, with “the exon 4 mutation causing c544C to T mutation with the protein going from arginine 182 to cysteine.”}

It is an interesting psychological challenge when, having lived a reasonably normal, healthy life, one is confronted with the knowledge that something has been quietly and consistently burrowing away, as it were, at one’s biological essence. It seems akin to a deceitful bodily self-affront. And yet, why should it not be so? We all – save in the farthest reaches of futuristic speculations – have to die of something; and the proverbial bus could despatch any of us at any time. But somehow there is a quiet finality to it all: the challenges, and possible end, that one may face are suddenly revealed in stark, undeniable simplicity. Given my age and the likely progress of the condition, I am perhaps approaching the end of the race, and a bell may signal the start of the final stretch at any time. The everyday term for the archetypal manifestation of a brain haemorrhage – a “stroke” – well reflects its characteristic suddenness, rather like the ominous appearance of a medieval executioner.

I find that I have a new, heightened sense of awareness. Occasional head pains – too minor and fleeting to be termed headaches – now take on a new significance. A momentary stumble, as I miss my footing, is now something that I note and remember, in case it becomes a frequent occurrence. A verbal hesitancy, if I have to search for the correct word, is no longer something casually ignored. Yet all such events are part and parcel of everyday life – who does not occasionally have a headache; who does not sometimes miss their footing; and who does not sometimes search for a word in their speech? Friends of a comparable age are kind enough to say that they experience similar events too, and I’m sure that they do. And yet, and yet …

There are, too – perhaps inevitably – associated feelings of guilt. The guilt may be unwarranted and illogical, but it exists nonetheless, albeit in a shadowy, background form. No moral blame can be attached when I inherited the gene, and none was involved when I passed it on, as I now know I have. An MRI scan of my elder son has revealed tell-tale signs of white matter lesions in his brain too. In his case, a decision needs to be made about whether he should seek genetic testing as final confirmation. There may be little point in this, and there are insurance implications too – so it’s not an easy decision for someone with family responsibilities. I acquired knowledge of my condition at age 60 – the
situation is different for someone in their early thirties, with children of their own. The burden is greater.

Diagnosis of a degenerative condition changes everything, but more so perhaps if the condition is a rare one, because it can be so unexpected. It can fracture plans and dreams, metaphorically knock you sideways, and require ongoing emotional investment as you try to assess what your next steps should be. Further, living with a progressive disease is a profound challenge not just for the affected individual but for his or her family too.

So, is it better to know or not know? Well, the answer may depend both on the medical condition and on an individual’s circumstances. In my case, I think it is a privilege as well as a burden. My diagnosis has not only helped explain what happened to my immediate forebears, but has also helped me to connect with them in a way that would not otherwise have been possible. I understand more now. And, although modern medicine cannot currently provide a cure, it can help mitigate the risks, and identify lifestyle choices that may optimise future wellbeing. Further down the line, my descendants may benefit from advances in gene therapy, which is already making significant strides forward. For my part, I’ll just try to maintain a full and active life, hope for the best ... and keep taking the tablets.